AMENDMENTS TO THE SPECIFICATION:

Please replace the specification with the following rewritten paragraphs.

Paragraph on page 1, lines 4-8 (paragraph [0001] of the published application):

This application is a continuation-in-part of ~~copending~~ application No. 09/385,219, filed August 27, 1999, now Patent No. 6,720,181, which claims benefit of priority under 35 U.S.C. § 119(e) to provisional application No. 60/098,355, filed August 28, 1998, provisional application No. 60/118,568, filed February 3, 1999, and provisional application No. 60/124,449, filed March 15, 1999, each of which is incorporated herein in its entirety.

Paragraph on page 5, lines 5-14 paragraph [0015] of the published application):

All well-characterized substrates of mammalian Fbp1 have a common destruction motif, DSGxxS (SEQ ID NO:94), and are recognized by Fbp1 only upon phosphorylation of the two serine residues present in this motif. There is, however, some recent evidence for additional mammalian substrates of Fbp1 lacking a completely conserved binding domain, such as ATF4 (Lassot, et al., 2001, Mol. Cell. Biol. 21:2192), Smad3 (Fukuchi, et al., 2001, Mol. Biol. Cell 12:1431), NFκB p105 (Orian, et al., 2000, EMBO J. 19:2580) and NFκB p100 (Fong and Sun, 2002, J. Biol. Chem. 277:22111). A conserved DSGxxS motif is present not only in Fbp1 substrates but also in certain regulators of Fbp1, such as hnRNP-U (Davis, et al., 2002, Genes Dev. 16:439), and in the HIV protein Vpu, which targets Fbp1 to a non-physiological substrate, CD4, only in virally infected cells (Margottin, et al., supra).

Paragraph on page 17, lines 8-28 (paragraph [0082] of the published application):

FIG. 37A-C. Binding of phosphorylated p27 to Skp2. **A.** A panel of in vitro translated [35S]FBPs were used in binding reactions with beads coupled to the phospho-peptide NAGSVEQT*PKKPGLRRRQT (SEQ ID NO:85), corresponding to the carboxy terminus of the human p27 with a phosphothreonine at position 187 (T*). Beads were washed with RIPA buffer and bound proteins were eluted and subjected to electrophoresis and autoradiography (Upper Panel). Bottom Panel: 10% of the in vitro translated [35S]FBP inputs. **B.** HeLa cell extracts were incubated with beads coupled to the phospho-p27 peptide (lane 2), an identical except unphosphorylated p27 peptide (lane 1) or the control phospho-peptide AEIGVGAY*GTVYKARDPHS (SEQ ID NO:90), corresponding to an amino terminal peptide of human Cdk4 with a phosphotyrosine at position 17 (Y*) (lane 3). Beads were washed with RIPA buffer and bound proteins were immunoblotted with antibodies to

the proteins indicated on the left of each panel. A portion of the HeLa extract (25 μg) was used as a control (lane 4). The slower migrating band in Cul1 is likely generated by the covalent attachment of a ubiquitin-like molecule, as already described for other cullins 48. **C.** One μl of in vitro translated [35S] wild type p27 (WT, lanes 1-4) or p27(T187A) mutant (T187A, lanes 5-6) were incubated for 30 minutes at 30¼C in 10 μl of kinase buffer. Where indicated, ~2.5 pmol of recombinant purified cyclin E/Cdk2 or ~1 pmole Skp2 (in Skp1/Skp2 complex) were added. Samples were then incubated with 6 μl of Protein-A beads to which antibodies to Skp2 had been covalently linked. Beads were washed with RIPA buffer and bound proteins subjected to electrophoresis and autoradiography. Lanes 1-6: Skp2-bound proteins; Lanes 7 and 8: 7.5% of the in vitro translated [35S] protein inputs.

Paragraph on page 25, lines 16-34 to page 26, lines 1-7 (paragraph [0101] of the published application):

Fig. 56 A-D: Fbp5/Emi1 is a bona fide substrate of β-Trcp1/Fbp1 in vivo and in vitro. A. Alignment of the amino acid regions corresponding to the putative β-Trcp1/Fbp1-binding motif in Fbp5/Emi1 orthologs and in previously reported β-Trcp1/Fbp1 substrates IkBα (Hs) (SEQ ID NO:95, β-catenin (Hs) (SEQ ID NO:96), Emi1 (Hs) (SEQ ID NO: 97, Emi1(Mm) SEQ ID NO: 98, Emi1(XI) (SEQ ID NO:99), Emi1(Dm) (SEQ ID NO:100). B. Wild type Fbp5/Emi1 is only stable in Fbp1–/– MEFs, whereas Fbp5/Emi1(S145A/S149A) mutant is stable both in Fbp1–/– and +/+ MEFs. MEFs were transfected with either myc-tagged wild type Fbp5/Emi1 (second panel from the top) or myc-tagged Fbp5/Emi1(S145A/S149A) mutant (bottom panel). Twenty-four hours after, cells were treated with nocodazole, round prometaphase cells were collected by mitotic shake-off and replated in the presence of cycloheximide. At the indicated times, MEFs were collected, lysed and extracts were subjected to immunoblotting with antibodies to myc (to detect exogenous Myc-tagged Fbp5) and Cul1 (as a loading control). C. Purified recombinant β-Trcp1/Fbp1 rescues the ability of an extract from Fbp1-/- MEFs to ubiquitinylate Fbp5/Emi1 in vitro. In vitro ubiquitin ligation of in vitro translated Fbp5 was carried out with extracts from wild type MEFs (lanes 1-4) or Fbp1-deficient MEFs in the absence (lanes 5-8) or in the presence of purified recombinant SCFFbp1 (9-12). The small bracket on the left side of the panels marks Fbp5/Emi1, which progressively up-shifted with time, likely because of phosphorylation events. The larger bracket marks a ladder of bands >50,000 corresponding to polyubiquitinylated Fbp5/Emi1. D. β-Trcp1/Fbp1 binding to Fbp5/Emi1 depends on the DSGxxS motif present in Fbp5. HeLa cells were transfected with an empty vector (lanes 1, 5

and 8), Flag-tagged β-Trcp1/Fbp1 (lane 2, 6-7, 9-10), Flag-tagged Fbw4 (lane 3), Flag-tagged Fbw5 (lane 4) alone or in combination with either myc-tagged Fbp5/Emi1 (lanes 5-6 and 8-9) or Fbp5/Emi1(S145A/S149A) mutant (lanes 7 and 10). Cells were lysed and extracts were either subjected to immunoprecipitation (IP) with a mouse anti-Flag antibody followed by immunoblotting analysis (IB), as indicated (lanes 1-7), or directly to immunoblotting to check levels of expression of wild type and mutant Fbp5/Emi1 proteins (lanes 8-10).

Paragraph on page 35, lines 3-34 to page 36, lines 1-5 (paragraph [0138] of the published application):

The determination of percent identity between two sequences can also be accomplished using a mathematical algorithm. A preferred, non limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul, 1990, Proc. Natl. Acad. Sci. USA 87:2264 2268, modified as in Karlin and Altschul, 1993, Proc. Natl. Acad. Sci. USA 90:5873 5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul, et al., 1990, J. Mol. Biol. 215:403 410. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al., 1997, Nucleic Acids Res. 25:3389 3402. Alternatively, PSI Blast can be used to perform an iterated search which detects distant relationships between molecules (Altschul et al., 1997, supra). When utilizing BLAST, Gapped BLAST, and PSI Blast programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used ~~(see http://www.ncbi.nlm.nih.gov)~~. Another preferred, non limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul, 1990, Proc. Natl. Acad. Sci. USA 87:2264, modified as in Karlin and Altschul, 1993, Proc. Natl. Acad. Sci. USA 90:5873. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul, et al., 1990, J. Mol. Biol. 215:403. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for

comparison purposes, Gapped BLAST can be utilized as described in Altschul, et al., 1997, Nucleic Acids Res. 25:3389. Alternatively, PSI Blast can be used to perform an iterated search which detects distant relationships between molecules (Altschul, et al., 1997, supra). When utilizing BLAST, Gapped BLAST, and PSI Blast programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used ~~(see http://www.ncbi.nlm.nih.gov)~~. Another preferred, non limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, 1988, CABIOS 4:11. Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used.

Paragraph on page 89, lines 12-20 (paragraph [0343] of the published application):

DNA database searches and analysis of protein motifs. ESTs (expressed sequence tags) with homology to FBP genes were identified using BLAST, PSI-BLAST ~~(http://www.ncbi.nlm.nih.gov/BLAST/)~~ and TGI Sequence Search (http://www.tigr.org/cgi-bin/BlastSearch/blast_tgi.cgi). ESTs that overlapped more than 95 % in at least 100 bps were assembled into novel contiguous ORFs using Sequencher 3.0. Protein domains were identified with ProfileScan Server ~~(http://www.isrec.isb-sib.ch/software/PFSCAN_form.html)~~, BLOCKS Sercher ~~(http://www.blocks.fhcrc.org/blocks_search.html)~~ and IMB Jena ~~(http://genome.imb-jena.de/cgi-bin/GDEWWW/menu.cgi)~~.

Paragraph on page 96, lines 16-34 to page 97, lines 1-4 (paragraph [0369] of the published application):

Unchecked degradation of cellular regulatory proteins (e.g., p53, p27, β-catenin) has been observed in certain tumors, suggesting the hypothesis that deregulated ubiquitin ligases play a role in this altered degradation (reviewed in Ciechanover, 1998, EMBO J, 17:7151). A well understood example is that of MDM2, a proto-oncogene encoding a ubiquitin ligase whose overexpression destabilize its substrate, the tumor suppressor p53 (reviewed by Brown and Pagano, 1997, Biochim Biophys Acta,1332:1). To map the chromosomal localization of the human FBP genes and to determine if these positions coincided with loci known to be altered in tumors or in inherited disease, fluorescence in situ hybridization (FISH) was used. The FBP1 gene was mapped and localized to 10q24 (Fig. 34A), FBP2 to 9q34 (Figure 34B),

FBP3a to 13q22 (Figure 34C), FBP4 to 5p12 (Figure 34D) and FBP5 to 6q25-26 (Figure 34E). FBP genes (particularly FBP1, FBP3a, and FBP5) are localized to chromosomal loci frequently altered in tumors ~~(for references and details see Online Mendelian Inheritance in Man database, http://www3.ncbi.nlm.nih.gov/omim/)~~. In particular, loss of 10q24 (where FBP1 is located) has been demonstrated in approx. 10 % of human prostate tumors and small cell lung carcinomas (SCLC), suggesting the presence of a tumor suppressor gene at this location. In addition, up to 7% of childhood acute T-cell leukemia is accompanied by a translocation involving 10q24 as a breakpoint, either t(10;14)(q24;q11) or t(7;10)(q35;q24). Although rarely, the 9q34 region (where FBP2 is located) has been shown to be a site of loss of heterozygosity (LOH) in human ovarian and bladder cancers. LOH is also observed in the region. Finally, 6q25-26 (where FBP5 is located) has been shown to be a site of loss of heterozygosity in human ovarian, breast and gastric cancers hepatocarcinomas, Burkitt's lymphomas, and parathyroid adenomas.

Paragraph on page 105, lines 31-34 to page 106, lines 1-8 (paragraph [0408] of the published application):

Antisense experiments were performed as described in (Yu, 1998, Proc. Natl. Acad. Sci. U. S. A. 95: 11324). Briefly, four oligodeoxynucleotides that contain a phosphorothioate backbone and C-5 propyne pyrimidines were synthesized (Keck Biotechnology Resource Laboratory at Yale University): (1) 5'-CCTGGGGGATGTTCTCA-3' (SEQ ID NO: 86) (the antisense direction of human Skp2 cDNA nucleotides 180-196); (2) 5'-GGCTTCCGGGCATTTAG-3' (SEQ ID NO: 87) [the scrambled control of (1)]; (3) 5'-CATCTGGCACGATTCCA-3' (SEQ ID NO: 88) (the antisense direction of Skp2 cDNA nucleotides 1137-1153); (4) 5'-CCGCTCATCGTATGACA-3' ~~(89)~~ (SEQ ID NO:89) [the scrambled control for (3)]. The oligonucleotides were delivered into HeLa cells using Cytofectin GS (Glen Research) according to the manufacturers instructions. The cells were then harvested between 16 and 18 hours postransfection.

Paragraph on page 117, lines 17-29 (paragraph [0450] of the published application):

The Fbp1 targeting vector was linearized and electroporated into D3 embryonic stem cells. Clones doubly resistant to G418 (300 μg/ml) and gancyclovir (2 μM) were tested for homologous recombination by Southern analysis. Two genomic probes were used to confirm that homologous recombination had occurred using HindIII or XbaI digests (in Fig. 52A, HindIII sites are indicated as "H" and XbaI sites as "X"). A neo^R gene probe was used to

insure that random integration of the targeting vector had not occurred elsewhere in the genome. Male chimaeras produced F1 agouti animals, 50% of which were F1 heterozygotes. Male and female F1 heterozygotes identified by Southern or genomic PCR analysis were interbred to produce F2 progeny. A genomic PCR assay (Fig. 52C) to detect the wild-type allele (372 bp) or the mutant Fbp1 allele (261 bp) was designed using a common D3 primer (5'CTTCCTTATCTAACAGAAGATGGA3') (SEQ ID NO:91) and the Fbp1 wild-type exon D1 primer (5'TCCTGACCATCCTCTCGATGAGC3') (SEQ ID NO:92) or the neoR gene L90 primer (5'TCTAATTCCATCAGAAGCTGACT3') (SEQ ID NO:93).

Paragraph on page 127, lines 7-15 (paragraph [0493] of the published application):

Fbp5 contains a DSGxxS (SEQ ID NO:94) Fbp1 binding domain (aa 145-149), which is conserved among species (from fly to human, Fig. 56A) and suggests that this protein might be a direct substrate of Fbp1. To test this possibility, MEFs were transfected with myc-tagged wild type Fbp5 or an Fbp5 mutant in which both serines of the DSGxxS (SEQ ID NO:94) motif had been mutated to alanine [Fbp5(Ser-145/149) mutant]. Cells were synchronized in prometaphase, and Fbp5 half-life was measured by the addition of cycloheximide. The measurements revealed that wild type Fbp5 was stabilized in Fbp1-/- cells, but not Fbp1+/+ cells (Fig. 56B, top panels). In contrast, the Fbp5(S145A/S149A) mutant was stable in both genotypes (Fig. 56B, bottom panels).